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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,053	10/19/2001	Apollon Papadimitriou	CIBT-P01-097	4732

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EXAMINER	
O HARA, EILEEN B	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 08/11/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,053	PAPADIMITRIOU ET AL.	
	Examiner	Art Unit	
	Eileen O'Hara	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,8,9,15 and 16* is/are pending in the application.

4a) Of the above claim(s) *9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,8,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-4,8,9,15 and 16* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *25 July 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on June 1, 2005 has been entered.

Claims Status

2. Claims 1-4, 8, 9, 15 and 16 are pending in the instant application. Claims 1, 8 and 15 have been amended, claims 7 and 11-14 have been canceled and claim 16 has been added as requested by Applicant in the Paper filed June 1, 2005.

Claim 9 is withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the Paper filed Nov. 30, 2003.

Claims 1-4, 8, 15 and 16 are currently under examination.

Withdrawn Objections and Rejections

3. Any objection or rejection of record which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 16 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Claim 16 encompasses a pharmaceutical composition comprising a buffer comprising 300 mmol/l arginine chloride. The specification on page 9 teaches that the buffer may comprise 300 mmol/l arginine chloride, but a search of the literature showed that buffers comprising arginine chloride have a significantly lower concentration of arginine chloride than 300 mmol/l. Michaelis et al., U.S. Patent No. 5,919,757, teach optimum levels of arginine chloride and other compounds in buffers, and that some buffer systems or pH values can lead to formation of aggregates and turbidities. At column 5, lines 13-29, Michaelis states:

"Arginine phosphate, arginine chloride and arginine citrate buffer is also used at a concentration of 2-100 mmol/l, preferably 5-80 mmol/l. The pH value of the liquid preparation containing arginine buffer is about 7-8, preferably 7-7.5.

The described selection of buffer systems according to the invention at physiologically tolerated pH values and physiologically tolerated concentrations is also a good idea and advantageous in the case of solutions of G-CSF prepared from lyophilisates or powders by redissolving.

Since mechanical agitation (shaking) is exerted when lyophilisates are redissolved it is important in this case to specifically select particular buffer systems and pH values. Selection of buffer systems or pH values that are not within the scope of the invention can lead to the formation of aggregates, turbidities and thus to a low quality product."

Additionally, in the examples in the specification, there is no arginine chloride present in the hedgehog compositions (Examples 1 and 2). Therefore, it is not predictable that this high a concentration of arginine chloride would be biologically compatible.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

It is acknowledged that the level of skill in the art is high. However, the prior art teaches that the optimum levels of arginine chloride in buffer systems is about 2-100 mmole/l, and that depending on the concentrations of components and pH of the buffer systems, aggregates can form, which would be biologically undesirable. Also, the specification does not disclose a working example in which hedgehog protein is contained in a buffer comprising 300 mmole/l arginine chloride. Therefore, it is not predictable that this high a concentration of arginine chloride would be desirable.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

5. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Pepinsky et al., U.S. Patent No. 6,444,793, filed 12/3/97, in view of Easton et al., U.S. Patent No. 4,614,794, issued Sept. 30, 1986, in view of Usala et al., U.S. Patent No. 6,231,881, filing date July 10, 1998, and further in view of Holly, U.S. Patent No. 4,518,579, May 21, 1985.

Claim 15 is drawn to a pharmaceutical composition containing hydrophobically modified hedgehog protein and a biodegradable protein as carrier, wherein the hedgehog protein is at a concentration of 0.1-100 mg/ml, wherein the composition is buffered in a range between 6 and 8, wherein the buffer comprises arginine chloride and potassium phosphate.

The teachings of Pepinsky et al., Easton et al. and Usala et al. were described in the previous office actions. Pepinsky et al., Easton et al. and Usala et al. do not teach that the buffer additionally comprises potassium phosphate.

Holly teaches an ophthalmic solution comprising a buffer of potassium phosphate (claim 5).

It would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to make a pharmaceutical composition comprising a

hydrophobically modified hedgehog protein, as taught by Pepinsky et al., using a collagen or collagen/alginate matrix of Easton et al., additionally adding a polar amino acid such as arginine, as taught by Usala et al., and adding potassium phosphate to the buffer, as taught by Holly. One of ordinary skill in the art would be motivated to add potassium phosphate to the buffer since it is a compound widely used in making buffers. There would be a reasonable expectation of success, since this compound has been used extensively and successfully for many years in buffer compositions.

Maintained Rejections

Double Patenting

6. Claims 1-4 and 8 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,207,718, for reasons of record in the Office Actions, Paper No. 10, at pages 5-6, and paper mailed Sept. 9, 2004 at pages 2-3.

Applicants on page 4 state that they will submit a terminal disclaimer, if necessary, upon indication of allowable subject matter. Until a terminal disclaimer is filed, the rejection is maintained.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person

having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4 and 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Pepinsky et al., U.S. Patent No. 6,444,793, filed 12/3/97, (provisionals filed 9/10/98, 6/17/98, 3/20/98 and 12/3/97) in view of Easton et al., U.S. Patent No. 4,614,794, issued Sept. 30, 1986, and further in view of Usala et al., U.S. Patent No. 6,231,881, filing date July 10; 1998, or Michaelis et al., U.S. Patent No. 5,919,757, for reasons of record in the previous Office Actions, Paper No. 10 at pages 7-11, paper mailed Sept. 9, 2004, at pages 3-5, paper mailed March 16, 2005 and below.

Applicants traverse the rejection on pages 4-5 of the response, and contend that the rejection is moot in light of the amended claims. Applicants maintain the arguments of record with respect to the combination of references which the Examiner alleges undermine the patentability of the claimed invention, and Applicants have amended the claims to more particularly point out the nature of the buffer for use in the presently claimed compositions. Specifically, Applicants have amended the claims to more particularly point out that the pharmaceutical compositions are buffered in arginine chloride, and dependent claim 16 recites a

particular exemplary arginine chloride concentration of 300 mmole/l. Applicants assert that the amended claims are nonobvious in view of the prior art which does not teach or suggest the claimed compositions buffered in arginine chloride either generally or at a specific concentration.

Applicants' arguments have been fully considered but are not deemed persuasive, for reasons of record in the previous office actions, and below.

Pepinsky et al. provides ample motivation for one of skill in the art to determine concentrations of hedgehog proteins, particular buffers, particular pH ranges and delayed release biodegradable proteins. Pepinsky et al. teaches that the half-life of hedgehog is very short after systemic application and that multiple injections are required to achieve a robust response to the protein and that the possibility of formulation in liposomes provides a means of achieving a response with fewer treatments (column 38, line 62 to column 39, line 1), and that the proteins can be administered locally to the site of bone fractures to help heal those fractures (column 39, lines 20-22). Since Easton teaches complexes having different stabilities, pore sizes and uses (column 3, line 47 to column 4, line 28), and that examples of such applications include media to be used in the controlled release of physiologically active compounds (column 5, lines 50-55), it would have been *prima facie* obvious to one of ordinary skill in the art to administer the hedgehog proteins of Pepinsky et al. in a carrier such as collagen that has been formulated to release the proteins slowly as taught by Easton. And since Usala et al. teach that arginine can increase the rigidity of the matrix, one of ordinary skill in the art would be motivated to make and use such complexes for local administration of hydrophobically modified hedgehog proteins, which could be made to allow diffusion of the protein at different rates and that had various

stabilities. Michaelis et al., U.S. Patent No. 5,919,757 also teaches (see rejection under 35 U.S.C. 112, first paragraph) that buffers can comprise arginine chloride. Claim 16 is not included in this rejection, since the art does not teach buffers comprising arginine chloride at a concentration of 300 mmol/l, and Michaelis et al. teach optimum concentrations lower than this (see rejection under 35 U.S.C. 112 first paragraph). The motivation to make such compositions is provided by Pepinsky's teachings that systemically administered hedgehog proteins have short half-lives and that local application without the need for frequent application would be desirable under certain circumstances. Although Pepinsky et al. do not specifically state that the specific compositions of the instant claims, Pepinsky et al. provide ample guidance on how to determine optimal pharmaceutical compositions, and that one of ordinary skill in the art would know how to make such determinations.

For these reasons, the rejection is maintained.

It is believed that all pertinent arguments have been answered.

Conclusion

8. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eileen B. O'Hara, whose telephone number is (571) 272-0878. The examiner can normally be reached on Monday through Friday from 10:00 AM to 6:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached at (571) 272-0829.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://portal.uspto.gov/external/portal/pair. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

Eileen B. O'Hara

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